HHS Public Access

Author manuscript

Epidemiol Infect. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Epidemiol Infect. 2018 August ; 146(11): 1350–1358. doi:10.1017/S0950268818001486.

Severe Morbidity Among Hospitalized Adults With Acute Influenza and other Respiratory Infections; 2014–15 and 2015–16

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SUMMARY

Our objective was to identify predictors of severe acute respiratory infection in hospitalized patients and understand the impact of vaccination and neuraminidase inhibitor administration on severe influenza. We analyzed data from a study evaluating influenza vaccine effectiveness in two Michigan hospitals during the 2014–2015 and 2015–2016 influenza seasons. Adults admitted to the hospital with an acute respiratory infection were eligible. Through patient interview and medical record review, we evaluated potential risk factors for severe disease, defined as ICU admission, 30-day readmission, and hospital length of stay. Two hundred of 1072 participants had PCR-confirmed influenza. Frailty score, Charlson score, and tertile of prior-year health care visits were associated with length of stay. Charlson score >2 (OR:1.6[1.0, 2.4]) was associated with ICU admission. Highest tertile of prior-year visits (OR:0.4[0.2, 0.7]) was associated with decreased ICU admission. Increasing tertile of visits (OR: 1.4[1.2, 1.8]) was associated with 30-day readmission. Frailty and prior-year health care visits were associated with 30-day readmission among influenza-positive participants. Neuraminidase inhibitors were associated with decreased length of stay among vaccinated participants with influenzaA (HR:1.6 [1.0, 2.4]). Overall, frailty and lack of prior-year health care visits were predictors of disease severity. Neuraminidase inhibitors were associated with reduced severity among vaccine recipients.

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Potential Conflicts of Interest. L. L has received grant support from AstraZeneca, Merck, Pfizer, eMaxHealth Inc., Policy Analysis Inc., Analytica Inc., and Xcenda Inc. for work unrelated to this report. E. T. M has received grant support from Merck and Pfizer for work unrelated to this report. A. S. M. has received grant support from Sanofi Pasteur and consultancy fees from Sanofi, GSK, and Novavax for work unrelated to this report. All other authors report no potential conflicts.

Previous Presentation of Data. These data has been presented, in part, as a poster presentation at ID Week in San Diego, California in October 2017 (abstract #1043).

INTRODUCTION

It is widely recognized that seasonal respiratory illness, which peaks in fall and winter in temperate regions, is associated with corresponding peaks in doctor's office visits and hospital admissions [1,2]. Numerous respiratory pathogens are associated with hospitalization; notably, influenza, human metapneumovirus, respiratory syncytial virus, rhinovirus, and parainfluenza virus; all of which cause similar symptoms [3]. However, influenza-associated illness accounts for a substantial proportion of these medical events [2,4]. Influenza is a viral pathogen that causes an estimated 12,000 to 56,000 deaths in the United States annually [5]. Influenza-related severe outcomes, such as death, ICU admission, or the need for invasive mechanical ventilation, generally occur in elderly individuals or individuals with numerous comorbidities; however, previously healthy adults are also at risk for serious illness [6,7].

During the 2009 influenza A(H1N1) pandemic, individuals thought to be at low risk for severe influenza, such as those under the age of 65 and without recognized underlying conditions, were hospitalized at a higher than expected rate [8]. During the pandemic, previously unknown risk factors for influenza severity were identified with morbid obesity being one of the most consistently identified factors [9,10]. In post-pandemic seasons the age of those hospitalized for influenza A(H1N1)pdm09 infection increased along with an increase in the severity of influenza-related pneumonia [11–13]. There was, paradoxically, a corresponding decrease in the use of antiviral treatment initially, though rates of treatment have since risen [13,14]. With the continued circulation of the A(H1N1) pandemic strain along with A(H3N2) and B viruses it is critical to identify and monitor groups at risk for severe disease in order to optimize strategies, including use of neuraminidase inhibitors and vaccine prioritization when the vaccine supply is limited, to prevent adverse outcomes.

In order to identify predictors of influenza and acute respiratory illness (ARI) severity and, specifically, to understand the impact of vaccination and neuraminidase inhibitor administration on illness severity, we present data from adults hospitalized with ARI from two hospitals in Southeast Michigan over the 2014–2015 and 2015–2016 influenza seasons. Severe outcomes evaluated include ICU admission, length of stay (LOS), and 30-day readmission.

METHODS

Participant enrollment, interview and specimen collection

Participants were adults hospitalized for ARI at University of Michigan Hospital (UMH, Hospital A) in Ann Arbor, Michigan and Henry Ford Hospital (HFH, Hospital B) in Detroit. Enrollment occurred from November 5th 2014 to March 6th 2015, and from January 11th 2016 to April 15th 2016. Staff reviewed electronic medical records (EMRs) daily to identify newly admitted patients (≤72 hours) with ARI as previously described [15]. Eligible participants were approached, and they or their proxy provided written consent for participation in the study. All study procedures were approved by the Institutional Review Boards of the University of Michigan Medical School and the Henry Ford Health System.

Patients were interviewed at enrollment to collect information about demographics, influenza vaccination status, general health status, illness characteristics, and subjective assessment of frailty (unexplained >10 pounds weight loss [yes/no], little energy for desired activities [yes/no], difficulty walking 100 yards [no difficulty…unable to do], difficulty carrying 10 pounds [no difficulty…unable to do] and frequency of low/moderate activity [more than once/week…hardly ever/never]). Number of health care encounters in the past year and evidence of neuraminidase inhibitor prescription from the study hospital admission were extracted from EMRs. Information about comorbid health conditions were also extracted to calculate the Charlson Comorbidity Index (CCI) for each patient. The following outcome variables were collected from the EMR: death, ICU admission, ventilator use, length of stay, and 30-day readmission. Outcomes that were experienced by more than 10 influenza-positive participants, including ICU admission, length of stay, and 30-day readmission, were used in models.

Laboratory Methods

Nasal and throat swabs collected at enrollment were combined and tested for influenza viruses using reverse transcriptase polymerase chain reaction (RT-PCR). All primers, probes and protocols were developed and provided by the Influenza Division of the CDC. They were designed for detection of universal influenza A and B, and for subtype and lineage identification. All tests were performed in the investigators' laboratory at the University of Michigan School of Public Health.

Influenza Vaccination Status

Individuals were considered vaccinated if they had documentation or plausible self-report of influenza vaccine receipt ≥14 days before illness onset. Documented vaccination status was determined based on documentation from the EMR or state immunization registry. Plausible self-report was defined as reporting both the approximate date and location of vaccination. Individuals were considered unvaccinated if they had no evidence of documentation of vaccination and self-reported no vaccination. Participants were excluded if they had an incomplete self-report of vaccination (e.g. missing date or location) and no additional documentation or if they were vaccinated <14 days before illness onset.

Statistical Methods

CCI scores were categorized as 0, 1, 2, or 3 or greater; high CCI was defined as greater than 2. Frailty was defined as the presence of up to 5 dichotomized variables taken from the enrollment interview that were summed and weighted by the number of questions answered, as a few participants either refused to answer or answered "don't know" to either one or two of the frailty questions [15,16]. Total prior-year health care visits were defined as all inpatient and outpatient visits for any reason to a UM or HF Health System affiliated clinic in the previous year. Tertiles of prior year health care visits among all participants were calculated, and the variable was expressed as either 0 visits, or visits falling into the first (1–8 visits), second (9–21 visits), or third (≥22 visits) tertile. Long length of stay was defined as length of stay of >8 days. When used as a continuous outcome, LOS was log-transformed and beta coefficients were analyzed as percent change of LOS.

Participants were compared in frequency models using Pearson χ^2 test or Fisher's exact test. Firth's penalized logistic regression models were used to predict the odds of severe illness by various risk factors. Firth's method was used to reduce small-sample bias and improve model fit in the context of quasi-separation. Hospital site (UMH or HFH), sex, age (18–49, 50–64, 65+), frailty score, and CCI>2 were included in adjusted models a priori. Tertile of prior-year health care visits was included based on their significance in univariate models; this variable was modeled categorically for the outcomes of ICU admission and hospital length of stay and ordinally for 30-day readmission due to the monotonic relationship between these variables. For analyses restricted to influenza A positive individuals, influenza A subtype, influenza vaccination were included as adjustment factors. Cox proportional hazard models, censoring on death, were used to estimate the impact of antiviral treatment on hospital length of stay. Neuraminidase inhibitor administration was modeled as a time varying covariate indicating the day in the hospital admission when participants were treated. The models were adjusted for covariates associated with increased hospital length of stay in the risk factor analysis, weighted frailty score and tertile of prior-year health care visits. All statistics were completed using SAS (release 9.4, SAS Institute). Statistical significance was defined as a 95% confidence interval that did not include the null value.

RESULTS

Demographics and Outcomes by Influenza Status

We enrolled 1199 adults with ARI; 727 from the 2014–2015 season and 472 from the 2015–2016 season. Eighty (7%) hospitalizations were excluded due to missing or incomplete information on vaccination status, influenza status, or Charlson score, leaving 1119 participants in the analysis.

Two-hundred sixteen (19%) participants had PCR-confirmed influenza virus infection. Influenza-positive participants were significantly less likely to have received influenza vaccines (Table 1). Half of participants had a CCI >2 but this percentage was significantly lower in individuals with influenza (41.2%) compared to those testing negative (52.2%). Among influenza positive participants there were 2 deaths, 22 ICU admissions, 10 invasive ventilations and 19 instances of long LOS (>8 days); these outcomes were observed in similar frequencies between the influenza positive and negative populations. Thirty-day readmission was significantly less frequent among influenza-positive participants compared to those testing negative (Table 1).

One-hundred and eleven participants were infected with influenza A(H3N2) viruses, 90 with influenza A(H1N1)pdm2009 and 15 with influenza B viruses; models restricted to influenza-positive individuals excluded individuals with influenza B virus infection. There was a higher frequency of influenza A(H1N1)pdm09 infection among participants who were 18–49 years old (37% with H1N1 vs. 26% with H3N2, p=0.10), though this difference was not statistically significant (Table 2). CCI (p=0.02), tertile of prior year health care visits (p=0.05) and vaccination status (p=0.02) were associated with influenza A subtype; individuals with a CCI of 0, no health care visits in the prior year and who were unvaccinated were more frequently infected with influenza A(H1N1)pdm09 (Table 2). A

higher percentage of participants infected with H1N1 were admitted to the ICU, put on an invasive ventilator, and had LOS >8 days compared to those infected with H3N2 (Table 2).

Models Predicting Severe ARI and Influenza-associated ARI

Higher frailty and increased tertile of prior-year health care visits were associated with increased 30-day readmission among influenza-positive participants (Table 3). Individuals with the highest tertile of prior-year health care visits had decreased odds of ICU admission compared to those with no prior-year visits regardless of influenza status (Table 3). Frailty score was associated with longer LOS among all participants but not among participants with influenza-associated ARI (Table 3).

Neuraminidase Inhibitor Prescription

One hundred fourty-seven (68%) influenza-positive participants were treated with neuraminidase inhibitors. Treatment varied by enrollment hospital; over 75% of influenza-positive patients from Hospital A were treated compared to only 57% from Hospital B (p=0.01) (Table 4). Neuraminidase inhibitor administration also varied by time from illness onset to admission; 73% of participants admitted within two days were treated compared to 59% of those admitted later (p=0.02) (Data not shown). Median length of stay was lower among those with timely antiviral treatment (2.0 days) compared to those with late antiviral treatment (3.0 days) or no treatment (3.0), however the median length of stay did not vary significantly.

Clinical testing for influenza varied significantly by enrollment hospital, 74% of influenza-positive participants from Hospital B by research testing received a clinical influenza test compared to 90% from Hospital A. Only 10% of participants from either hospital without a clinically positive influenza test were treated with neuraminidase inhibitors (Data not shown).

The influenza-positive population was further stratified by vaccination status. Vaccinated individuals who were treated with neuraminidase inhibitors had a significantly reduced LOS ($HR_{discharge}$:1.6, 95% CI: 1.0, 2.4], p=0.04) compared to those who were untreated (Table 5). Other severe outcomes were not evaluated in this analysis due to insufficient sample size.

DISCUSSION

Our study identified risk factors for severe influenza-associated ARI and all-cause ARI among hospitalized patients over two influenza seasons. Given that viral etiology is often unknown at admission when many treatment decisions are made, it is important to understand severity of ARI of all causes in the hospital. Of note, 65% of participants where tested clinically for influenza and the majority of these tests were initiated the day of or the day after hospital admission. Despite the timely testing, it may take many hours for PCR results to be available to the clinician and rapid influenza tests are known for their low specificity. For these reasons, treatment decisions should be made before viral etiology is known in most cases. Higher frailty score was associated with longer LOS, and having 0 prior-year health care visits was associated with higher odds of ICU admission. Frailty is a well-known predictor of severity and death, especially among the elderly, though many

studies do not consider frailty when studying influenza severity [17–19]. The increased severity among those without prior-year health care visits may indicate that individuals who are unlikely to seek care present to the hospital with the most severe illnesses. Increased health care visits over the prior year were also associated with increased, rather than reduced, 30-day readmission indicating that 30-day readmission may be, in part, a measure of underlying chronic conditions [20].

We evaluated the impact of vaccination and neuraminidase inhibitor administration on influenza severity. Neuraminidase inhibitors were significantly associated with decreased LOS among vaccinated individuals only after stratification by vaccination status. While the association between neuraminidase inhibitor administration and reduced influenza severity has been emphasized, the interaction between vaccination and neuraminidase inhibitors is not well documented or understood [21,22]. Though this result offers an interesting potential relationship between antiviral treatment, vaccination, and influenza severity, the extremely small sample size in this stratified population necessitates repeated demonstration of this association in larger, future studies.

In light of this result and other evidence in the literature, it is critical that hospitalized influenza-positive patients are treated with neuraminidase inhibitors [22,23]. We found that just 67% of participants with PCR-confirmed influenza were prescribed neuraminidase inhibitors though treatment is recommended for all hospitalized patients with suspected or confirmed influenza. Treatment varied significantly by enrollment hospital; over 40% of influenza-positive participants at Hospital B did not receive neuraminidase inhibitors, compared to 23% at Hospital A. While all participants are tested for influenza by our research team, not every patient receives a clinical influenza test during their hospital stay. This appeared to impact treatment decisions, as very few individuals without a clinically positive influenza test were treated despite the recommendation that hospitalized individuals with suspected influenza be treated empirically.

These numbers indicate a need to continue public health messaging directed at nurses and physicians to encourage empiric treatment and to keep influenza on the list of possible diagnoses during influenza season. Additionally, participants were less likely to be treated if they were admitted to the hospital >2 days after symptom onset. This reflects the widely held opinion that antiviral drugs are only effective within 2 days of symptom onset. While studies have shown that effectiveness is higher when neuraminidase inhibitors are given promptly, there is evidence among hospitalized patients with influenza that treatment within 5 days of symptom onset improves survival [21,22,24].

Continued interest in the potential for vaccination to reduce influenza severity stems from the vaccine effectiveness (VE) estimates from the 2014–15 influenza season, which primarily consisted of influenza A viruses that were antigenically drifted from the Northern Hemisphere vaccine strains [15,25]. VE estimates from the 2014–15 season were higher in hospital studies than in ambulatory care studies, where they were not significantly different from zero [15,26,27]. This could indicate that influenza vaccination reduces severity as well as incidence; this hypothesis has been previously evaluated but results are mixed [28–31]. We did not find an association between severity and vaccination. Observational studies of

severity, such as ours, as well as evaluations of interventions such as vaccination are often impacted by confounding by indication and other challenges.

Overall, the small number of influenza-positive participants in this study led to reduced power, which may explain the few significant predictors of influenza severity. The in-hospital observational nature of the study complicated our ability to study some commonly used severity endpoints such as mechanical ventilation and death. Additionally, selection into this study depended on hospital admission prior to enrollment, potentially increasing the number of older individuals with comorbidities who are more likely to be admitted to the hospital with a less severe disease. We accounted for this in our analysis by adjusting for age, CCI, and prior-year health care visits, but residual confounding is always a concern. In addition, when calculating the tertile of prior-year health care visits, we could only access visits within the hospital study sites or their associated outpatient clinics, and the majority of individuals who had no visits did not get their regular care within these two systems. However, when the population was restricted to those who did get regular care at our study sites in a sensitivity analysis, the trends of increased severity among those with no prior-year visits remained.

In conclusion, we identified frailty and number of prior-year health care visits as predictors of all-cause and influenza-associated ARI severity. Our finding that vaccinated patients who received neuraminidase inhibitors had decreased LOS needs confirmation from future studies, but also adds to the evidence that administration of neuraminidase inhibitors to hospitalized patients reduces influenza severity and reinforces current treatment recommendations in the hospital [23,32–34].

Acknowledgments

Financial Support

This work was supported by the Centers for Disease Control and Prevention [U01 IP000974-01, U01 IP000474].

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Table 1

Demographics and Outcomes of Hospitalized Adults with ARI by Influenza Status

	Total N=1119	Influenza Positive N=216	Influenza Negative N=903	P Value[3]
Characteristics	N (Column %)	N (Column %)	N (Column %)	
Sex				0.68
Male	501 (44.7%)	94 (43.5%)	407 (45.1%)	
Female	618(54.8%)	122 (56.5%)	496 (54.9%)	
Age				0.44
18–49	323 (28.9%)	67 (31.0%)	256 (28.3%)	
50–64	415 (37.1%)	72 (33.3%)	343 (38.0%)	
≥65	381 (34.0%)	77 (35.7%)	304 (33.7%)	
Race[1]				0.62
White (Non-Hispanic)	583 (52.7%)	114 (54.0%)	469 (52.3%)	
Black (Non-Hispanic)	392 (35.4%)	76 (36.0%)	316 (35.3%)	
Other	132 (11.9%)	21 (10.0%)	111 (12.4%)	
Site of Enrollment				0.47
Hospital A	636 (56.8%)	118 (54.6%)	518 (57.4%)	
Hospital B	483 (43.2%)	98 (45.4%)	385 (42.6%)	
Year				0.12
2014–2015	664 (59.3%)	118 (54.6%)	546 (60.5%)	
2015–2016	455 (40.7%)	98 (45.4%)	357 (39.5%)	
Charlson Score				0.01
0	119 (10.6%)	33 (15.3%)	86 (9.5%)	
1	283 (25.3%)	62 (28.7%)	221 (24.5%)	
2	157 (14.0%)	32 (14.8%)	125 (13.8%)	
≥3	560 (50.0%)	89 (41.2%)	471 (52.2%)	
Frailty Score (median(IQR))		0.25 (0.0–0.50)	0.40 (0.20–0.60)	0.04
BMI Category[2]				0.51
<18.5	42 (3.9%)	4 (1.9%)	38 (4.3%)	
18.5–24.9	267 (24.7%)	53 (25.7%)	214 (24.5%)	
25–29.9	284 (26.3%)	53 (25.7%)	231 (26.4%)	
30–39.9	315 (29.1%)	65 (31.6%)	250 (28.6%)	
≥40	173 (16.0%)	31 (15.1%)	142 (16.2%)	
Number of Healthcare Visits (Tertiles)				0.61
0	128 (11.4%)	28 (13.0%)	100 (11.1%)	
1	349 (31.2%)	72 (33.3%)	277 (30.7%)	
2	318 (28.4%)	60 (27.8%)	258 (28.6%)	
3	324 (29.0%)	56 (25.9%)	268 (29.7%)	
Vaccination Status				<0.01

	Total N=1119	Influenza Positive N=216	Influenza Negative N=903	P Value[3]
Vaccinated	750 (67.0%)	113 (52.3%)	637 (70.5%)	
Unvaccinated	369 (33.0%)	103 (47.7%)	266 (29.5%)	
Death	15 (1.3%)	2 (1.0%)	13 (1.4%)	0.56
ICU	126 (11.3%)	22 (10.2%)	104 (11.5%)	0.58
Invasive Ventilator	48 (4.3%)	10 (4.6%)	38 (4.2%)	0.78
LOS >8 Days	108 (9.7%)	19 (8.8%)	89 (9.9%)	0.63
30 day Readmission	167 (14.9%)	16 (7.4%)	151 (16.7%)	<0.01

[1] 12 individuals have missing Race information

[2] 38 individuals have missing BMI information

[3] P values are from chi square tests or Fisher's exact tests when appropriate

Table 2

Demographics and Outcomes of Enrolled Patients Hospitalized with Influenza A Associated ARI by Subtype

	Total N=201	H3N2 N=111	H1N1N=90	
Characteristics	N (Column %)	N (Column %)	N (Column %)	P Value[3]
Sex				0.20
Male	90 (44.8%)	43 (48.7%)	43 (47.8%)	
Female	111 (55.2%)	68 (61.3%)	47 (52.2%)	
Age				0.10
18–49 y	62 (30.8%)	29 (26.1%)	33 (36.7%)	
50–64 y	68 (33.8%)	36 (32.4%)	32 (35.6%)	
≥65 y	71 (35.3%)	46 (41.4%)	25 (35.2%)	
Race[1]				0.22
White (Not Hispanic)	106 (53.8%)	63 (57.3%)	43 (49.4%)	
Black	71 (36.0%)	34 (30.9%)	37 (42.5%)	
Other	20 (10.1%)	13 (11.8%)	7 (8.0%)	
Site of Enrollment				0.29
Hospital A	111 (55.2%)	65 (58.6%)	46 (51.1%)	
Hospital B	90 (44.8%)	46 (41.4%)	44 (48.9%)	
Charlson Score				0.02
0	31 (15.4%)	10 (9.0%)	21 (23.3%)	
1	59 (29.3%)	39 (35.1%)	20 (22.2%)	
2	27 (13.4%)	13 (11.7%)	14 (15.6%)	
≥3	84 (41.8%)	49 (44.1%)	35 (38.9%)	
Frailty Score (median(IQR))	0.25 (0.0,0.40)	0.20 (0.0–0.5)	0.40 (0.0–0.40)	0.89
BMI Category[2]				0.11
<18.5	4 (1.7%)	4 (3.6%)	0 (0.0%)	
18.5–24.9	47 (24.0%)	24 (21.8%)	23 (28.4%)	
25–29.9	49 (25.1%)	33 (30.0%)	16 (19.7%)	
≥30	91 (49.2%)	49 (44.6%)	42 (51.9%)	
Year				<0.01
2014–15	107 (53.2%)	107 (96.4%)	0 (0.0%)	
2015–16	94 (46.8%)	4 (3.6%)	90 (100.0%)	
Total Number of Healthcare Visits In the Last Year (Tertiles)				0.05
0	25 (12.4%)	8 (7.2%)	17 (18.9%)	
1	64 (31.8%)	34 (30.6%)	30 (33.3%)	
2	58 (28.9%)	34 (30.6%)	24 (26.7%)	
3	54 (26.9%)	35 (31.5%)	19 (21.1%)	
Vaccination Status				0.02
Vaccinated	106 (52.7%)	67 (60.4%)	39 (43.3%)	

	Total N=201	H3N2 N=111	H1N1N=90	
Unvaccinated	95 (46.1%)	44(39.6%)	51 (56.7%)	
Death	2 (1.0%)	1 (0.9%)	1 (1.1%)	1.00
ICU	20 (10.0%)	7 (6.3%)	13 (14.4%)	0.06
Invasive Ventilator	9 (4.5%)	1 (0.9%)	8 (8.9%)	0.01
LOS >8 Days	18 (9.0%)	5 (4.5%)	13 (14.4%)	0.02
30 day Readmission	16 (8.0%)	10 (9.0%)	6 (6.7%)	0.61

[1] 4 individuals are missing race information

[2] 10 individuals are missing BMI information

[3] P values reflect results of Pearson Chi-square tests or Fisher's exact test when appropriate. P values for continuous variables represent results of Wilcoxon tests

Table 3

Predictors of Severe Disease in Participants with All-Cause ARI and in Patients with Influenza A associated ARI[1]

	ARI (N=1072)			Influenza A Positive (N=188)		
	ICU (OR, 95% CI)	**LOS (Percent Change, 95% CI)**	**30 Day Readmission (OR, 95% CI)**	**ICU (OR, 95% CI)**	**LOS (Percent Change, 95% CI)**	**30 Day Readmission (OR, 95% CI)**
Predictors						
Male Sex	1.5 (1.0, 2.2)	6.1 (−0.5, 13.1)	1.1 (0.8, 1.6)	0.7 (0.3, 1.8)	−5.0(−19.2, 11.7)	0.4 (0.1, 1.4)
Age						
18–49	1.0	0.0	1.0	1.0	0.0	1.0
50–64	1.0 (0.6, 1.6)	3.6 (−4.4, 12.3)	0.9 (0.6, 1.3)	1.1 (0.3, 3.6)	3.2 (−16.1, 26.9)	1.5 (0.3, 7.7)
≥65	1.0 (0.6, 1.6)	0.4 (−7.7, 9.1)	0.6 (0.4, 1.0)	1.0 (0.3, 3.4)	6.6 (−13.8, 31.9)	1.2 (0.3, 6.2)
Site of Enrollment						
Hospital A	1.0	0.0	1.0	1.0	0.0	1.0
Hospital B	0.8 (0.5, 1.2)	−0.7 (−7.3, 6.2)	1.4 (1.0, 2.1)	0.7 (0.2, 2.0)	−8.1 (−23.2, 9.9)	2.7 (0.9, 9.0)
Charlson Score >2	1.5 (1.0, 2.3)	21.7 (13.3, 30.7)	1.8 (1.2, 2.7)*	1.6 (0.5, 5.7)	8.5 (−11.0, 32.2)	1.1 (0.3, 4.2)
Vaccination	–	–	–	1.0 (0.3, 3.1)	−6.1 (−22.4, 13.6)	0.9 (0.3, 3.5)
Frailty Score[2]	1.5 (0.8, 3.0)	22.7 (9.3, 37.5)*	1.4 (0.8, 2.5)	1.0 (0.1, 6.1)	31.4 (−4.5, 80.9)	8.9 (1.2, 78.0)*
Total Visits[3] (Tertiles)			1.5 (1.2, 1.8)*			2.5 (1.2, 5.8)*
0	1.0	0.0		1.0	0.0	
1	0.6 (0.4, 1.1)	−18.8 (−21.1, −1.7)*		0.3 (0.1, 1.0)*	−11.7 (−33.1, 16.6)	
2	0.6 (0.3, 1.0)	−9.3 (−18.9, 1.6)		0.2 (0.0, 0.8)*	−4.2 (−28.3, 28.0)	
3	0.3 (0.2, 0.7)*	−11.2 (−21.3, 0.2)		0.1 (0.0, 0.8)*	−10.0 (−35.1, 24.9)	
Influenza A Subtype						
H3N2	–	–	–	1.0	0.0	1.0
H1N1	–	–	–	1.9 (0.7, 5.2)	11.1 (−5.7, 30.9)	0.8 (0.3, 2.4)

[1] Adjusted models contain male sex, age group, enrollment site, Charlson score, weighted frailty score, total annual healthcare visits, and influenza status. Influenza A subtype and vaccination were also included in models restricted to influenza A positive adults.

[2] OR and percent changes reflect the impact of a one-unit increase in weighted frailty score.

[3] Total number of annual healthcare visits is modeled categorically except in models predicting 30-day readmission where it is modeled ordinally and OR represent change in odds for a one tertile increase

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* indicates significance at the 5% confidence level

Table 4

Demographics by Antiviral Prescription Timing Among Participants with Laboratory Confirmed Influenza

	Timely Antivirals[1] N=86	Late Antivirals N=61	No Antivirals N=69	P Value[4]
Characteristics	N (Row %)	N (Row %)	N (Row %)	
Sex				0.75
Male	40 (42.6%)	26 (27.7%)	28 (29.8%)	
Female	46 (37.7%)	35 (28.7%)	41 (33.6%)	
Age				0.31
18–49	31 (46.3%)	21 (31.3%)	15 (22.4%)	
50–64	27 (37.5%)	21 (29.2%)	24 (33.3%)	
≥65	28 (36.4%)	19 (24.7%)	30 (39.0%)	
Race[2]				0.21
White	51 (44.7%)	32 (28.1%)	31 (27.2%)	
Black	30 (39.5%)	19 (25.0%)	27 (35.5%)	
Other	4 (19.0%)	8 (38.1%)	9 (42.9%)	
Site of Enrollment				0.01
Hospital A	54 (45.8%)	37 (31.4%)	27 (22.9%)	
Hospital B	32 (32.6%)	24 (24.5%)	42 (42.9%)	
Year				0.24
2014–2015	42 (35.6%)	33 (28.0%)	43 (36.4%)	
2015–2016	44 (44.9%)	28 (28.6%)	26 (26.5%)	
Influenza Type/Subtype				0.23
A/H3N2	37 (33.3%)	35 (31.5%)	39 (35.1%)	
A/H1N1	42 (46.7%)	24 (26.7%)	24 (26.7%)	
B	7 (46.7%)	2 (13.3%)	6 (40.0%)	
Charlson Score				0.36
0	17 (51.5%)	8 (24.2%)	8 (24.2%)	
1	17 (27.4%)	21 (33.9%)	24 (38.7%)	
2	14 (43.7%)	9 (28.1%)	9 (28.1%)	
≥3	38 (42.7%)	23 (25.8%)	28 (31.5%)	
Frailty Score	0.20 (0.0–0.40)	0.40 (0.20–0.60)	0.40 (0.20–0.60)	0.20
Obese[3]				0.22
Yes	39 (40.6%)	31 (32.3%)	26 (27.1%)	
No	43 (39.1%)	26 (23.6%)	41 (37.3%)	
Number of Health Care Visits (Tertiles)				0.52
0	11 (39.3%)	8 (28.6%)	9 (32.1%)	
1	28 (38.9%)	15 (20.8%)	29 (40.3%)	
2	23 (38.3%)	21 (35.0%)	16 (26.7%)	
3	24 (42.9%)	17 (30.4%)	15 (26.8%)	

	Timely Antivirals[1] N=86	Late Antivirals N=61	No Antivirals N=69	P Value[4]
Characteristics	**N (Row %)**	**N (Row %)**	**N (Row %)**	
Vaccination Status				0.85
Yes	46 (40.7%)	30 (26.6%)	37 (32.7%)	
No	40 (38.8%)	31 (30.1%)	32 (31.1%)	
Length of Stay (median, IQR)	2.0 (2.0–4.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.17

[1] Timely antivirals refers to antivirals within 2 days of symptom onset

[2] 5 individuals are missing race information

[3] 10 individuals are missing BMI information

[4] P values are from chi square tests or Fisher's exact tests when appropriate

Table 5

Hazards of Discharge Related to Antiviral Treatment Timing

	Overall (N=201)		Vaccinated (N=106)		Unvaccinated (N=95)	
Predictors	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**
Antiviral Treatment	1.1 (0.8, 1.5)	0.44	1.6 (1.0, 2.4)	0.04	0.9 (0.5, 1.4)	0.52
Frailty Score	0.5 (0.3, 1.0)	0.04	0.6 (0.3, 1.3)	0.17	0.5 (0.2, 1.2)	0.11
Total Visits (Tertiles)						
Tertile 0	ref		Ref		ref	
Tertile 1	1.6 (1.0, 2.7)	0.05	0.5 (0.1, 1.6)	0.23	1.6 (0.9, 2.9)	0.09
Tertile 2	1.3 (0.8, 2.1)	0.32	0.3 (0.1, 1.0)	0.05	1.3 (0.7, 2.4)	0.40
Tertile 3	1.5 (0.9, 2.4)	0.13	0.4 (0.2, 1.2)	0.09	1.6 (0.8, 3.5)	0.21

[1]Models contain all predictors in the table